

RECEIVED

OCT 05 2001

TECH CENTER 1600/2900



REMARKS

Initially, Claims 1-3 and 5-9 were rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which is not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

At page 3 and 4 of the Office Action, the Examiner suggested that the terms "pharmaceutically" and "pharmaceutical" be deleted from the claims as they represent an implied assertion of therapeutic efficacy.

Applicants point out that they have conducted receptor binding assays. The biological efficacy of compounds believed to be effective as tachykinin receptor antagonists may be confirmed by employing an initial screening assay which measures binding to NK-1 and NK-2 receptor sites. Assays useful for evaluating tachykinin receptor antagonists are well known in the art. See, e.g., J. Jukic, et al. *Life Sciences*, 49:1463-1469 (1991); N. Rouissi, *Biochemical and Biophysical Research Communications*, 176:894-901 (1991); D. Aharony, Isolation and Characterization of Neurokinin A Receptor cDNAs From Guinea Pig Lung and Rabbit Pulmonary Artery. *J. Recept. Res.*, 14:399 (1994). R. Catalioto, Independent Coupling of the Human Tachykinin NK₂ Receptor to Phospholipases C and A₂ in Transfected Chinese Hamster Ovary Cells, *Naunyn-Schmiedeberg's Arch. Pharm.*, 358:395-403 (1998). The antagonist activity at the NK-2 receptor of compounds of the present invention has been determined on the rabbit isolated pulmonary artery and the hamster isolated trachea preparations, two bioassays endowed with two putative NK-2 receptor subtypes. Notwithstanding, to overcome the Examiner's rejection, the terms "pharmaceutically" and "pharmaceutical" have been deleted from the aforementioned claims.

Applicants thank the Examiner for suggestions on amending the claims which are incorporated herein. An Abstract of the Disclosure has been added. In Claim 1, line 1, the term "monocyclic compounds" has been changed to the singular. Claims 1 and 2 have been amended to recite standard Markush language. Further, as suggested by the Examiner, Claims 10-13 have been amended to recite a "method of use" and Claim 15 has been added.

Turning to the substantive matters raised, at page 5 of the Office Action

Claims 1-2 were rejected under 35 U.S.C. §103 as being unpatentable over Kitakabake. Specifically, the Examiner stated that Claim 1 excludes the compound cyclo-Val-Val-Phe-Phe but does not exclude three other peptides which thereby renders Claims 1 and 2 obvious.

Applicant respectfully transgresses the rejection and requests reconsideration thereof.

Not only does the cited reference fail to disclose the invention as presently claimed, it refers to nonanalogous art. Literature pertaining to peptides for prevention of the gushing of beer is irrelevant for judging the inventiveness of the present NK-2 antagonists. Further, Kitakabake was published in 1979. For the past 22 years, it has not been obvious to modify Kitakabake to produce the compounds of the present invention. In fact, the field of NK-2 receptor antagonists has only developed over the last 10 years with the discovery of the first NK-2 antagonists around 1991.

The present invention is distinctly different from Kitakabake, which does not teach or address main features of the Applicant's invention. Notwithstanding, no teaching is provided that would motivate anyone to modify Kitakabake.

The present invention represents a significant advantage over the prior art and avoids disadvantages of the prior art compositions. The prior art discloses cyclic hexapeptides, bicyclic hexapeptides and cyclic hexapeptideptides with NK₂ activity. However, there remains a need for more potent and selective NK₂ receptor antagonists. The pA₂ of between 5 and 9 indicates that the compounds of the present invention are potent and selective NK-2 receptor antagonists. These compounds are structurally diverse from the prior art in that they have a lower molecular weight and are monocyclic with only four bifunctional residues linked together via peptide or pseudo peptide bonds. Such activity could not be predicted from the prior art which contains no teaching to suggest same.

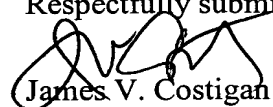
The prior art reference cannot be easily modified to include the unique structural and functional advantages described in the present invention. The elements of the present invention are neither disclosed nor addressed by the prior art.

Accordingly, it is urged that the unique structural and functional composition of the present application is unobvious. Given the aforementioned distinctions, it is maintained that the Kitakabake reference does not teach or suggest the present

invention. For these reasons, it is requested that the rejections to the present claims be withdrawn.

In view of the foregoing, an early and favorable action is earnestly solicited.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "James V. Costigan", is written over the typed name.

Registration No. 25,669

Hedman & Costigan, P.C.
1185 Avenue of the Americas
New York, N.Y. 10036
(212) 302-8989



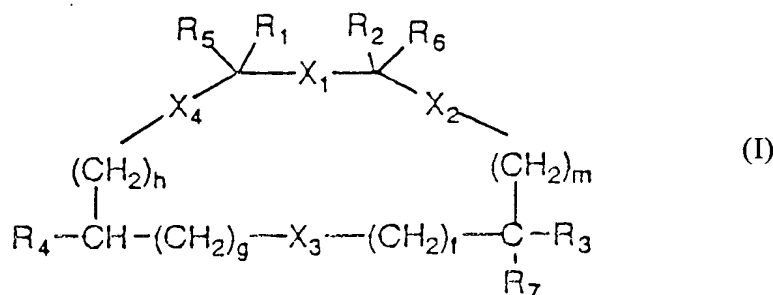
Version with Markings to Show Changes Made:

TECH CENTER 1600/2900

OCT 05 2001

RECEIVED

1. (Amended) A [M]monocyclic compound[s] having the general form (I):



in which:

X_1, X_2, X_3, X_4 , which may be the same or different from one another, [represent a group chosen from among] is selected from the group consisting of -CONR-, -NRCO-, -OCO-, -COO-, -CH₂NR-, -NR-CH₂- [,] and CH₂-CH₂, where R is H or a C₁₋₃ alkyl or benzyl;

f, g, h, m, which may be the same or different from one another, represent a number [chosen from among] selected from the group consisting of 0, 1 and 2;

R_1 and R_2 , which may be the same or different from one another, represent a -(CH₂)_r-Ar group, where r= 0, 1, 2 and where Ar is an aromatic group [chosen from among] selected from the group consisting of: benzene, naphthalene, thiophene, benzothiophene, pyridine, quinoline, indole, furan, benzofuran, thiazole, benzothiazole, imidazole, and benzo-imidazole, [the] said Ar group being possibly substituted with a maximum of [2] two residues [chosen from among] selected from the group consisting of C₁₋₃ alkyl or halo-alkyl, C₁₋₃ alkoxy, C₂₋₄ amino-alkoxy, halogen, OH, NH₂ [,] and NR₁₃R₁₄ where R₁₃ and R₁₄, which may be the same or different from one another, represent hydrogen or C₁₋₃ alkyl;

wherein R₃ [represents a group chosen from among] is selected from the group consisting of:

-hydrogen,

-linear or branched alkyl having the formula C_nH_{2n+1}, with n= 1-5, cyclo-alkyl or alkylcyclo-alkyl groups having the formula C_nH_{2n-1}, with n= 5-9,

-(CH₂)_r-Ar₁ group, where r= 0, 1, 2 and where Ar₁ is an aromatic group [chosen from among] selected from the group consisting of: benzene, naphthalene, thiophene,

benzothiophene, pyridine, quinoline, indole, furan, benzofuran, thiazole, benzothiazole, imidazole, and benzo-imidazole, [the] said Ar₁ group being possibly substituted with a maximum of [2] two residues [chosen from among] selected from the group consisting of C₁₋₃ alkyl or halo-alkyl, C₁₋₃ alkoxy or amino-alkoxy, halogen, OH, NH₂ [,] and NR₁₃R₁₄, where R₁₃ and R₁₄, which may be the same or different from one another, represent hydrogen or C₁₋₃ alkyl;

wherein R₄ [represents a group chosen from among] is selected from the group consisting of:

-hydrogen or C₁₋₆ alkyl,

- L-Q, where L is a chemical bond or a linear or branched C₁₋₆ alkyl residue and Q is [a group chosen from among] selected from the group consisting of:

i) H, OH, OR₉, NH₂, NR₉R₁₀, guanidine, sul[ph]fate, phosphonate[,], and phosphate where R₉ and R₁₀, which may be the same or different from one another, represent a hydrogen C₁₋₃ alkyl group, C₁₋₃ hydroxyalkyl, C₁₋₃ dihydroxyalkyl, C₁₋₃alkyl-CONHR₁₂, C₁₋₃alkyltetrazole, C₁₋₃alkyl-COOH or wherein R₉R₁₀ joined together form with the N-atom a saturated 4-6 membered heterocycle possibly containing a further heteroatom [chosen in] selected from the group consisting of N, O[,], and S and

wherein R₁₂ is a mono-, di-, tri-glycosidic group possibly protected with one or more C₁₋₃-acyl groups or substituted with amino-groups or C₁₋₃ acylamino-groups;

ii) COOH, tetrazole, SO₂NH₂, SO₂NHCOOR₈, CONHR₈, NHCOR₈, where R₈ represents a linear or cyclic C₁₋₆ alkyl chain containing one or more polar groups [chosen from among] selected from the group consisting of: OH, NH₂, NR₁₅R₁₆, COOH, CONHR₁₂, PO₃H, SO₃H[,], and OR₁₁ and where R₁₅ and R₁₆, which may be the same or different from one another, represent a hydrogen or C₁₋₃ alkyl group, and where R₁₁ is a C₁₋₃ alkyl or C₂₋₄ amino-alkyl chain, R₁₂ is a mono-, di-, tri-glycosidic group possibly protected with one or more C₁₋₃acyl groups or substituted with amino-groups or C₁₋₃acylamino-groups or R₁₅R₁₆ joined together form with the N-atom a saturated 4-6 membered heterocycle possibly substituted with C₁₋₃alkyl-groups or with saturated 4-6 membered heterocycle-groups containing at least an N-atom;

iii) COOR₁₇, CONHR₁₂, OR₁₂ where R₁₂ is a mono-, di-, tri-glycoside group possibly protected with one or more C₁₋₃ acyl groups or substituted with amine or C₁₋₃ acylamine groups and R₁₇ is a group R₁₂ as above defin[in]ed or a group C₁₋₃ alkyl, C₁₋₃ alkylphenyl, wherein the phenyl-group can be substituted with a group OH, NO₂, NH₂, CN, CH₃, Cl, Br;

R₅, R₆, R₇, which may be the same or different from one another, represent a hydrogen or C₁₋₃ alkyl group; [their pharmaceutically acceptable salts, their enantiomers and mixture thereof] or an acceptable salt or enantiomer thereof.

2. (Amended) Compounds according to Claim 1, in which:

f, g, h, m, which may be the same or different from one another, may be 0 or 1;

R₁ and R₂ which may be the same or different from one another, represent the side chain of a natural amino acid [chosen from among] selected from the group consisting of tryptophan, phenylalanine, tyrosine[,] and histidine, or the side chain of a non-natural amino acid [chosen in] selected from the group consisting of:

tryptophan and phenyl alanine, either mono- or di-substituted with residues [chosen from among] selected from the group consisting of C₁₋₃ alkyl or halo-alkyl, C₁₋₃ alkoxy or amino-alkoxy, halogen, OH, NH₂[,] and NR₁₃R₁₄, where R₁₃ and R₁₄, which may be the same or different from one another, represent a hydrogen or C₁₋₃ alkyl group;

R₃ [represents a group chosen from among] is selected from the group consisting of:

– linear or branched alkyl having the formula C_nH_{2n+1} with n = 1-5 ([chosen in] selected from the group consisting of methyl, ethyl, propyl, isopropyl, n-butyl[,] and t-butyl) cycloalkyl or alkylcycloalkyl of formula C_nH_{2n-1} with n = 5-9 ([chosen in a] selected from the group consisting of: cyclopentyl, cyclohexyl[,] and methylcyclohexyl)

–(CH₂)_r-Ar₁, where r = 1 or 2 and where Ar₁ is an aromatic group [chosen in] selected from the group consisting of: α-naphthyl, β-naphthyl, phenyl, indole, [the] said Ar₁ group being possibly substituted with a maximum of [2] two residues [chosen in] selected from the group consisting of: C₁₋₃ alkyl, CF₃, C₁₋₃ alkoxy, Cl, F, OH[,] and NH₂;

R₄ represents an L-Q group where:

L is a chemical bond or CH₂, and

Q is [a group chosen from among] selected from the group consisting of:

- OH, NH₂, NR₉R₁₀ [,] and OR₁₁, and where R₉ and R₁₀, which may be the same or different from one another, represent a hydrogen or C₁₋₃ alkyl group, C₁₋₃hydroxy alkyl, C₁₋₃dihydroxyalkyl, C₁₋₃alkyl-CONHR₁₂ (wherein R₁₂ is a monoglycosidic group derived from D or L pentoses or [hesoxes] hexoses ([chosen in] selected from the group consisting of ribose, arabinose, glucose, galactose, fructose, glucosamine[,] and galactosamine and their N-acetylated derivatives)), C₁₋₃alkyltetrazole, C₁₋₃alkyl-COOH or wherein R₉R₁₀ are joined together to form with the N atom a morpholine or a piperidine ring and where R₁₁ is a C₁₋₃ alkyl chain, or a C₂₋₄ amino-alkyl chain;
- NHCOR₈ wherein R₈ is a cyclohexane containing from 2 to 4 OH groups, a C₁₋₆alkylchain containing a polar group (chosen in the group consisting of NH₂, COOH, CONHR₁₂, (wherein R₁₂ is as hereabove defined) or [1,4']bipiperidine)
- COOH, COOR₁₇ or CONHR₁₂, wherein R₁₂ is as hereabove defined and R₁₇ is as R₁₂ or a group 4-nitrobenzyl.
- R₅, R₆, R₇ are H[.]

in which the carbon atom that carries the substituents R₃ and R₇ has configuration R.

3. A [C]compound[s] according to Claim 2[, as specified below] selected from:

- (a) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH₂C₆H₅)-CH₂-NH]}
- (b) Cyclo{-Suc-Trp-Phe-[(S)-NH-CH(CH₂C₆H₅)-CH₂-NH]}
- (c) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH₂C₆H₁₁)-CH₂-NH]}
- (d) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH₂C₆H₄(4-OCH₃))-CH₂-NH]}
- (e) Cyclo{-Suc-Trp(5F)-Phe-[(R)-NH-CH(CH₂C₆H₅)-CH₂-NH]}
- (f) Cyclo{-Suc-Trp(Me)-Phe-[(R)-NH-CH(CH₂C₆H₅)-CH₂-NH]}
- (g) Cyclo{-Suc-Phe(3,4-Cl)-Phe-[(R)-NH-CH(CH₂C₆H₅)-CH₂-NH]}
- (h) Cyclo{-Suc-Trp-Phe(3,4-Cl)-[(R)-NH-CH(CH₂C₆H₅)-CH₂-NH]}
- (i) Cyclo{-Suc-Trp-Tyr-[(R)-NH-CH(CH₂C₆H₅)-CH₂-NH]}
- (j) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH₂C₆H₃-3,4-diCl)-CH₂-NH]}

- (k) Cyclo {-Suc-Trp-Phe-[(R)-NH-CH(CH₂C₆H₄-4-OH)-CH₂-NH]}
- (l) Cyclo {-Suc-Trp-Phe-[(R)-NH-CH(CH₂-CH₂-C₆H₅)-CH₂-NH]}
- (m) Cyclo {-Suc-Trp-Phe-[(R)-NH-CH(CH₂-2-naphthyl)-CH₂-NH]}
- (n) Cyclo {-Suc-Trp-Phe-[(R)-NH-CH(CH₂-indol-3-yl)-CH₂-NH]}
- (o) Cyclo {-Suc-Trp-Phe-[(R)-NH-CH(CH₂-5-F-indol-3-yl)-CH₂-NH]}
- (p) Cyclo {-Suc-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₄-3-F)-CH₂-NH]}
- (q) Cyclo {-Suc-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₃-3,4-diF-CH₂-NH)-]}
- (r) Cyclo {-Suc-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₄-4-CF₃-CH₂-NH)-]}
- (s) Cyclo {-Suc-Trp-Phe-[(R)-NH-CH₂-CH(CH₂C₆H₅)-NH]}
- (t) Cyclo {-Suc-Trp-Phe-[(S)-NH-CH₂-CH(CH₂C₆H₅)-NH]}
- (u) Cyclo {-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-(CH₂)₃CO-}
- (v) Cyclo {-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-N(CH₃)]-(CH₂)₃CO-}
- (w) Cyclo {-Suc[1(S)-NH₂]-Trp-Phe-[(R)NH-CH(CH₂-C₆H₅)-CH₂NH]-}
- (x) Cyclo {-Suc[1(R)-NH₂]-Trp-Phe-[(R)NH-CH(CH₂-C₆H₅)-CH₂NH]-}
- (y) Cyclo {-Suc[2(S)-NH₂]-Trp-Phe-[(R)NH-CH(CH₂-C₆H₅)-CH₂NH]-}
- (z) Cyclo {-Suc[2(R)-NH₂]-Trp-Phe-[(R)NH-CH(CH₂-C₆H₅)-CH₂NH]-}
- (aa) Cyclo {-Suc[1(S)-NH(CH₃)]-Trp-Phe-[(R)NH-CH(CH₂-C₆H₅)-CH₂NH]-}
- (ab) Cyclo {-Suc[1-COO(CH₂-C₆H₄-4-NO₂)]-Trp-Phe-[(R)NH-CH(CH₂-C₆H₅)-CH₂NH]-}
- (ac) Cyclo {-Suc(1-COOH)-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]}
[Cyclo {-Suc(1-COOH)-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]}]
- (ad) Cyclo {-Suc(1-OH)-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]}
- (ae) Cyclo {-Suc(2-COOH)-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]}
- (af) Cyclo {-Suc(2-OH)-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]}
- (ag) Cyclo {-Suc[1(S)-(2H-tetrazolyl-5-ylmethyl)amino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-}. TFA
- (ah) Cyclo {-Suc[1(S)-(morpholin-4-yl)]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-}. TFA
- (ai) Cyclo {-Suc[1(S)-N(CH₃)₂]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-}. TFA
- (aj) Cyclo {-Suc[1(S)-(piperidin-4-yl)]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-}. TFA
- (ak) Cyclo {-Suc[1(S)-(N(CH₂CH₂OH)₂)]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-

NH]}.TFA

(al) Cyclo{-Suc[1(S)-(N(CH₂CH(OH)CH₂OH)]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-}.TFA

(am) Cyclo{-Suc[1(S)-(3-carboxypropanoyl)amino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-}.

(an) Cyclo{-Suc[1(S)-[3-N'-β-D-glucopiranos-1-yl)-carboxamidopropanoyl]amino]-Trp-Phe-[(R)NH-CH(CH₂-C₆H₅)-CH₂NH]-}

(ao) Cyclo{-Suc[1(S)-[(carboxymethyl)amino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-}. TFA

(ap) Cyclo{-Suc[1(S)-[N'-β-D-glucopiranos-1-yl)-carboxyamidomethyl]amino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-} TFA

(aq) Cyclo{-Suc[1(S)-(chiny)amine]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-}

(ar) Cyclo{-Suc[1(S)-(4-aminobutanoyl)amino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-} TFA

(as) Cyclo{-Suc[1(S)-[1,4')bipiperidin-1-yl]acetamido]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-} TFA

(at) Cyclo{-Suc[1-N-(β-D-glucopiranos-1-yl)-carboxyamido]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-}

(au) Cyclo{-Suc[1(S)-[N'-(2-N-acetyl-β-D-glucopiranos-1-yl)-carboxyamido]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-}.

5. (Amended) A [Pharmaceutical] composition[s containing as active the compounds] comprising a compound of general formula (I) according to Claim 1 in combination with a [pharmaceutically acceptable] suitable carrier or excipients.

6. (Amended) A [Pharmaceutical] composition[s] according to Claim 5, [to be used] adapted for use as tachykinin antagonists.

7. (Amended) A [Pharmaceutical] composition[s] according to Claim 6, [to be used] adapted for use as antagonists of the human NK-2 receptor.

8. (Amended) A [Pharmaceutical] composition[s] according to Claim 7, [to be used] adapted for use in the treatment of the bronchospastic and inflammatory component of asthma, coughing, pulmonary irritation, intestinal spasms, spasms of the biliary tract, local spasms of the bladder and of the ureter during cystitis, and kidney infections and colics.

9. (Amended) A [Pharmaceutical] composition[s] according to Claim 7, [to be used] adapted for use as anxiolytics.

10. (Amended) [Use of] A method of antagonizing tachykinin in a mammal in need thereof comprising contacting tachykinin peptide receptors with a compound according to Claim 1 for a time and under conditions effective to antagonize said [as] tachykinin [antagonist] receptors.

11. (Amended) [Use of] A method of antagonizing an NK-2 receptor in a mammal in need thereof comprising contacting an NK-2 receptor with a compound according to Claim 1 for a time and under conditions effective to antagonize an [as] NK-2 [antagonist] receptor.

12. (Amended) [Use of] A method of antagonizing an NK-2 receptor in a mammal afflicted with asthma comprising contacting an NK-2 receptor with a compound according to Claim 1 for a time and under conditions effective to antagonize an NK-2 receptor [in the treatment of the bronchospastic and inflammatory component of asthma, coughing, pulmonary irritation, intestinal spasms, spasms of the biliary tract, local spasms of the bladder and of the ureter during cystitis, and kidney infections and colics] .

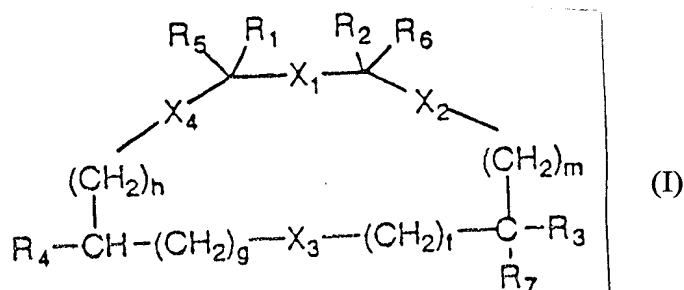
13. (Amended) [Use of a composition] A method of antagonizing an NK-2 receptor in a mammal afflicted with an anxiety disorder comprising contacting an NK-2 receptor with a compound according to Claim 1 for a time and under conditions effective to antagonize [as] an NK-2 receptor [antagonist for the treatment of anxiety syndromes] .



09/355210
RECEIVED
OCT 05 2001
TECH CENTER 1600/2900

ABSTRACT OF THE DISCLOSURE:

Disclosed are monocyclic compounds containing four bifunctional residues linked together via peptide or pseudopeptide bonds of the general formula (I)



having tachykinin receptor antagonist activity. In particular, compounds of formula I are shown to be neurokinin-2 (NK-2) antagonists useful in the treatment or prevention of disorders of the central nervous system, inflammatory diseases, asthma, or pain.